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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,566	04/02/2001	Peter W. Laird	47675-18	2853

22504 7590 05/04/2006

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,566	LAIRD ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/10/2006 has been entered.

2. Currently, claims 1-19 are pending in the instant application. The following objections and rejections are either newly applied or are reiterated. Response to applicant's arguments follow, where appropriate. This action is NON- FINAL.

Withdrawn Rejections and Objections

3. The objection to the specification made at section 4 of the previous office action is withdrawn in view of the amendment to the sequence listing to delete SEQ ID NOS 67 (that is, previously submitted SEQ ID NO: 67 filed 8/9/2004), 68-71 and 73-76. The declaration of Peter Laird submitted under 37 CFR 1.132 as well as the response's arguments made at page 8, 2nd full para, are persuasive to overcome the objection with regard to SEQ ID NOS 66 and 72 (now SEQ ID NO: 67). Accordingly, SEQ ID NO: 66 and the sequence now termed "SEQ ID NO: 67" in the amendment filed 2/10/2006 have been entered as supported by the originally filed specification and claims.

4. The rejection of claims 1-20, made under 35 USC 112/first paragraph with regard to New Matter is withdrawn in view of the amendments to the claims as well as the response's arguments made at page 9 (first full para that is: lines 5-9).

Maintained Rejections

5. The rejection of claims 1-3, 5-8, and 10 under 35 USC 102 (b) as anticipated by Iacopetta as defined by Kyrgidis made at section 9 of the previous office action, and the rejection of claims 15-19 under 35 USC 103(a) as unpatentable over Iacopetta as defined by Kyrgidis in view of Huang, at section 10 of the previous office action are reiterated and maintained herein. The response's arguments have been thoroughly reviewed but were found unpersuasive as the preamble continues to recite "an esophageal cancer related condition". The rejections can be overcome by amending the preamble in claim 1 to agree with the final process step of the claim (see scope of enablement rejection below).

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Note: the following rejection is applied based on a reassessment of the state of the art and the teachings in the specification.

6. Amended claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing or prognosing esophageal cancer, esophageal dysplasia, esophageal metaplasia, Barrett's intestinal tissue, Barrett's esophagous, or combinations thereof comprising obtaining a sample of esophageal tissue comprising genomic

DNA, performing a methylation assay of the tissue sample wherein the methylation assay determines the methylation state of the sequence of the MYOD1 gene delimited by the primer pair of SEQ ID NO: 7 and 8 as compared to a normal control DNA sample, and diagnosing or prognosing esophageal cancer, esophageal dysplasia, esophageal metaplasia, Barrett's intestinal tissue, Barrett's esophagous, or combinations thereof , based, at least in part, on the detection of hypermethylation of the sequence of the MYOD1 gene delimited by the primer pair of SEQ ID NO: 7 and 8 as compared to a normal control DNA sample, does not reasonably provide enablement for diagnosis or prognosis of esophageal cancer, esophageal dysplasia, esophageal metaplasia, Barrett's intestinal tissue, Barrett's esophagous, pre-cancerous conditions in normal esophageal squamous mucosa or combinations thereof , or any esophageal cancer related condition by detecting hypermethylation, or determining the hypermethylation state of, in 'at least one" CpG sequence in any region of the MYOD1 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. [Statements made in the previous office action with regard to enabled methods of diagnosing breast cancer, colorectal carcinoma, and Embryonal rhabdomyosarcoma based on the state of the prior art, are reiterated herein].

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman.

> They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are now broadly drawn to diagnosis or prognosis of esophageal cancer or any esophageal cancer related condition or pre-cancerous conditions in normal esophageal squamous mucosa by determining the hypermethylation state of "at least one" genomic CpG sequence. The claims encompass a method of making any diagnostic or prognostic prediction or determination of any esophageal cancer related condition by determining the hypermethylation state of a single genomic CpG sequence in any region of the MYOD1 gene. It is noted that diagnosis or prognosis is not dependent on hypermethylation, but rather that analysis determine the hypermethylation state. The claims therefore, continue to broadly encompass diagnosis based on any methylation state.

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches that CpG islands in the promoter region of the MYOD1 gene delimited by the primer pair of SEQ ID NO: 7 and 8 were hypermethylated in intestinal metaplasia tissue as compared to normal esophageal tissue (see page 36, lines 4-6). The specification teaches that increases in MYOD1 methylation were found in esophageal adenocarcinoma, Barrett's esophagus, and dysplasia (see Fig. 1). The specification further teaches that MYOD1 hypermethylation was correlated with increases in tumor stage (see Fig. 4, page 38). The specification is silent, however, to an association between methylation of

MYOD1 and diagnosis or prognosis, even at least in part, "any" esophageal cancer related condition. Esophageal cancer related conditions include not only Barrett's esophagous, Barrett's intestinal metaplasia, and esophageal dysplasia, but also GERD (gastroesophageal reflux disease), Tylosis (A genetic disorder characterized by thickening of the palms and soles, white patches in the mouth, and a very high risk of esophageal cancer), Esophageal Achalasia (loss of peristalsis), celiac disease, Plummer-Vinson syndrome and Esophageal webs (structural abnormalities), which are risk factors or diseases associated with esophageal cancer. The specification is silent with regard to any association between methylation of even a single CpG dinucleotide in MYOD1, and the large number of diseases or disorders encompassed by *any* "esophageal cancer related condition" or any "precancerous conditions in the normal esophageal squamous mucosa". Further, the specification provides no predictable correlation that hypermethylation of the MYOD1 gene is associated, diagnostic, or prognostic for any esophageal cancer related condition or any pre-cancerous conditions in normal esophageal squamous mucosa based on an association between esophageal cancer and certain esophageal cancer related condition, such as Barrett's esophagous. A large number of distinct disorders are encompassed by "esophageal cancer related conditions" and "pre-cancerous conditions in normal esophageal squamous mucosa", which are not necessarily predictive of ultimate Barrett's esophagous or esophageal carcinoma. These disorders only represent a small subset of risk factors, and would not necessarily be associated with methylation differences in the MYOD1 gene as compared to "normal" esophageal tissue or esophageal tissue from subjects not suffering from any such disorder.

Additionally, the claims encompass diagnosis or prognosis based on the methylation state of one genomic CpG sequence. Such recitation encompasses an association between the methylation status of a single CpG dinucleotide and diagnostic or prognostic significance. However, the specification teaches that aberrant hypermethylation in cancer cells often occurs at CpG islands (page 1). This finding, strongly corroborated by the teachings in the art, suggest that the methylation of a single CpG island would not be predictably diagnostic or prognostic of any disease or disorder, including esophageal cancer, Barrett's intestinal tissue, Barrett's esophagous, esophageal metaplasia or dysplasia, or any "esophageal cancer related condition" or "pre-cancerous conditions in normal esophageal squamous mucosa". CpG islands represent stretches of genomic DNA with a certain GC content, as defined by the specification. The specification teaches, however, that CpG dinucleotides outside of an island are presumably normally methylated (see page 33, last line). Given that the specification provides an association between *hyper*methylation of CpG islands in the sequence of the MYOD1 gene delimited by the primer pair of SEQ ID NOS 7 and 8, the specification provides no predictable correlation that the methylation status of any single CpG dinucleotide in any region of the MYOD1 gene, would be diagnostic or prognostic of any disease, let alone esophageal cancer or any "esophageal cancer related condition" or other conditions encompassed by the broadly claimed invention.

The state of the prior art and the predictability or unpredictability of the art:

The disclosure of the prior and post filing date art teach that conditions that are considered risk factors for esophageal carcinoma, do not necessarily indicate that a patient will necessarily develop esophageal cancer. For example, Kyrgidis (Kyrgidis et al; Journal of

Surgical Research, vol. 125, pages 189-212, 2005) teaches that while Barrett's esophagus represents the most serious histological consequence of gastroesophageal reflux disease (GERD), it only develops in 5-10% of patients with GERD. Streitz (Streitz et al; Annals of Thoraci Surgery, vol. 59, pages 1604-1609, 1995) teaches that there is a wide range of reported cancer risks in achalasia patients, from zero to 33 times that of the normal population (see abstract). Thus, as exemplified by the teachings in the art, the recitation of any "esophageal cancer related condition" and "pre-cancerous conditions in normal esophageal squamous mucosa" encompasses a large group of diseases and disorders, which are not necessarily predictive of eventual Barrett's esophagus, or esophageal cancer. The art is silent with regard to a predictable association between methylation status of MYOD1 and the broadly encompassed recitation of "esophageal cancer related condition".

Dependent claims 3-10 and 18-19, although reciting the primers of SEQ ID NO: 7 and 8 and the probe of claim 9, are not limited to the sequence delimited by the primer pair as a larger region, which encompasses the indicated SEQ ID NOS could be broadly "defined" by or broadly "associated" with the SEQ ID NOS. However, the art does not support the idea that all contiguous CpG islands are associated with cancer. For example, in CACNAIG (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions were found to behave differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 4, 8 behaved differently and regions 5, 6, 7 behaved differently than regions 1-3. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNAIG appears to be behave independently (page 4538, col. 1).

Given the lack of guidance in the specification as to other regions in the MYOD1 gene which contain hypermethylated CpG islands diagnostic or prognostic for the conditions set forth in the claims, the skilled artisan would be unable to predict whether other CpG islands in the MOD1 gene act in an independent manner.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Therefore, based on the limited guidance in the specification, and the unpredictability taught in the art, it would require undue experimentation for one of skill in the art to practice the invention as broadly as it is claimed. The skilled artisan would have to screen a large number of patients with the many different types of "esophageal cancer related conditions" or "pre-cancerous conditions in normal esophageal squamous mucosa" to determine a predictable correlation between the "state of hypermethylation" of at least one genomic CpG sequence in any region of the MYOD1 gene was diagnostic or prognostic as broadly claimed. Additionally, the skilled artisan would have to perform an exhaustive analysis of CpG dinucleotides within the MYOD1 gene to determine if *any* CpG dinucleotide could be used for diagnostic or prognostic purposes. Based on the teachings of the art and the specification that CpG dinucleotides outside of CpG islands tend to be methylated and that CpG islands can behave independently with regard to hypermethylation in cancer, the skilled artisan would be required to perform a large amount of unpredictable trial and error analysis to establish that *any* CpG dinucleotide in any region of the

MYOD1 gene would be diagnostic or prognostic of the claimed disorders or any "esophageal cancer related condition" or "pre-cancerous conditions in normal esophageal squamous mucosa". Further, based on the unpredictability in the art and the lack of guidance in the specification with regard to diagnosis of any type of esophageal cancer related condition or "pre-cancerous conditions in normal esophageal squamous mucosa", it is clear that the skilled artisan would be required to perform additional unpredictable trial and error analysis to determine whether hypermethylation status of MYOD1 could be used to diagnose or prognose *any* esophageal cancer related condition or "pre-cancerous conditions in normal esophageal squamous mucosa". It also is noted that the amended claims, although recited "state of hypermethylation" do not set forth any specific methylation alteration in the MYOD1 gene from an esophageal tissue sample. The claims merely set forth an invitation to experiment as they leave it up to the skilled artisan to determine the state of hypermethylation (eg: no hypermethylation) of MYOD1 compared to methylation in a control subject is indicative of esophageal cancer or esophageal cancer related condition.

Based on the lack of guidance in the specification and the unpredictability taught in the art, undue experimentation would be required of the skilled artisan to practice the invention as broadly as it is claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples other than for Barrett's esophagus - intestinal metaplasia, adenocarcinoma, or esophageal dysplasia, the unpredictable teachings in the art balanced only

against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

7. The response asserts that the amendment is responsive to the rejection set forth in the previous office action, and particularly points to the addition of the term "hypermethylation". The rejection is maintained for the reasons set forth above. Further, it is noted that the claims do not require diagnosis or prognosis, based at least in part, on the detection of hypermethylation, but broadly recite that it is based on the state of hypermethylation, thus still encompassing any methylation state (ie: no hypermethylation).

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 10/240,126. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are coextensive in scope encompassing methods of diagnosing esophageal cancer related conditions based on the methylation of MYOD1. The SEQ ID NOS 1-60 in the instant specification and the '126 application are same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Jehanne Sitton
Primary Examiner
Art Unit 1634

5/1/06